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EXAMINER	
KOSAR, AARON J	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,712	TAKEO ET AL.	
	Examiner	Art Unit	
	Aaron J. Kosar	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-16 and 19-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group III (claims 17-18) and species (d) cerebrovascular hyperpermeability in the reply filed on November 7, 2007 is acknowledged. Applicant has also amended the claims by adding new claims 25-27. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-16 and 19-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 7, 2007.

Claims 17, 18, and 25-27 are pending and have been examined on their merits.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on April 13, 2006 is in compliance with the provisions of 37 CFR 1.97. Please note that the references have been considered to the extent provided in the English language, in tables and graphs, as referenced by Applicant in the original disclosure, or as cited by the Examiner (PTO-892 form). Specifically, reference AF (JP 2003-506368 A) has not been considered and has been lined-through. Accordingly, the information disclosure statement is being considered by the examiner and has been placed in the Application file.

Claim Objections

Claims 25-27 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The claims are objected to

because the limitations of learning function, memory function, and dementia improvements in claims 25-27 are not further limiting of claim 18, a method of *inhibiting (cerebro)vascular hyperpermeability* or the component compositions/active steps therein. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 18, and 25-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification - while being enabling for a method of treating a mammal suffering from a cerebral embolism-induced cerebrovascular hyperpermeability said embolism induced by injection into and occlusion of the right external carotid or pterygopalatine arteries, and said method comprising injecting into the cerebral ventricle a concentration of hepatocyte growth factor (HGF) in an amount sufficient to ameliorate symptoms associated with embolism-induced damage for example symptoms including loss in memory or learning deficiencies - does not reasonably provide enablement for all neurological deficiencies, disorders, treatments, modes of administration, or formulations of HGF. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention *commensurate in scope* with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 858 F.2d

731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The nature of the invention and the breadth of the claims:

The claims are generally drawn to the method comprising any mode of administering HGF to a mammal; however, the claims have a greater breadth than what is supported by the specification.

The state of the prior art and the predictability or unpredictability of the art:

The state of the prior art is such that HGF is known GOHDA (U: PTO-892 10/09/2007: E Gohda, et al., J. Clin Invest. 1988, 81(2), 414–419 (e.g. Abstract)).).

BOJE (Current Protocols in Neuroscience. 2001, supplement 15, unit 7.19.1-7.1.39) teaches the utility of rat models and anatomy of the right common carotid artery and the

interrelation with the occipital, internal carotid, pterygopalatine arteries (figures 7.19.2 and 7.19.3).

DATE (Date, I., et al. Biochemical and Biophysical Research Communications, 2004, 319 1152-1158.) teaches that injection of microspheres into the internal carotid artery of rats induces a variety of manifestations by teaching that the selected animals used in a water maze test were categorized/scored and preselected such that the most severely deficient rats as measured by paucity of movement, truncal curvature, and forced circling during locomotion were selected. This constitutes a teaching that microsphere-induced embolism administered through the internal carotid artery resulted in motor skill deficiencies (mobility, posture, coordination deficiencies respectively). Date also teaches that (c. May 11,2004) that HGF "should be evaluated as a prospective agent for the therapy against ischemic brain injuries, including cerebral infarction and vascular dementia"(page 1157, concluding ¶). This constitutes a teaching that treating (vascular) dementia with HGF and as a result the effects thereof was unresolved in the art at the time of Date.

SEKIGUCHI (Sekiguchi, M., et al. Experimental Neurology. 2005, 191, 266-275.) teaches that microsphere-induced cerebral ischemia may affect the ipsilateral cerebellum and medulla and the contralateral cerebellum (¶1, page 274). Sekiguchi also teaches that microsphere injection produces "widespread formation of small emboli and multiple infarct areas in the brain...including cerebral cortex, hippocampus, corpus striatum, midbrain, cerebellum, and medulla"(page 270, right column, ¶1-2). This constitutes a teaching that microsphere-induced damage is primarily, but not isolated to, the immediate efferent arterial vicinity of the vascular injection site.

GUARCH (Guarch, J. et al. International journal of Geriatric Psychiatry, 2004, 19, 352-358.) teaches the unpredictability of memory loss and dementia by teaching that memory loss (a decline in memory function) is a "manifestation of the normal aging process" and, independent of age, may also have neither cognitive nor functional impairments. Guarch also teaches that memory loss may be asymptomatic with respect to memory loss, especially in subjective memory loss subjects where 75-90% may be asymptomatic for other deficiencies (¶3, page 353).

OVERSHOT (Overshot, R. and Burns, A. Psychiatry 2007, 6(12), 491-497.) teaches that delirium may be superimposed upon an underlying dementia and that delirium has similar symptoms as dementia (memory impairment, disorientation, and/or altered psychomotor activity) (page 491, ¶3; table 1). Overshot teaches that it is essential to assess multiple areas of cognition (page 492, last ¶) and that a full history and mental state examination should be performed although Overshot teaches that the Mini-Mental State Examination (MMSE) is commonly used. The teachings of overshot constitute a teaching (1) that dementia is complex and requires multiple indices to properly resolve versus other conditions and various forms of dementia (e.g. delirium, depression, Alzheimer's, etc.) and (2) that the tests used to diagnose and resolve dementia and/or memory are question-answer based assessments (MMSE is a 30-point/question test)(page 494, ¶2). Overshot does not teach any adapted methods for assessing memory function, learning, or dementia in non-human subjects.

ISHIKAWA (Ishikawa, K, et al. "Hippocampal degeneration inducing impairment of learning in rats: model of dementia?" Behavioral Brain Research, 1997 (Feb), 83(1-2), 39-44.) teaches that single evaluation of a drug with one learning paradigm was difficult to justify that a drug is effective for dementia (abstract). Ishikawa also teaches that "the criterion of dementia is

cognitive deficits which are manifested as memory impairment and other disturbances..", that "memory itself is not a simple phenomenon" and that "memory impaired in dementia is [declarative], which is only observed in humans" (page 39; page 43, ¶ 2). Ishikawa further teaches that learning experiments using animal models one must be careful, because the criteria for the condition, dementia, includes not only memory impairment, but also disturbances of the central nervous function, such as aphasia, apraxia, and agnosia (page 43, ¶2).

Although HGF is taught to be an angiogenic polypeptide and to have utility, the mechanism between HGF and complex conditions appears to not be fully resolved in the prior art especially for dementia, including vascular dementia (Date, see above) or the complex conditions including memory and dementia (Overshot, see above) which may be affected by angiogenesis or some as of yet unidentified property of HGF upon the affected tissues. Since the mechanisms of inhibiting declining memory and dementia and assessing the conditions is largely unresolved as discussed above, the art is therefore highly unpredictable.

Furthermore, pharmaceutical therapies are unpredictable for the following reasons: (1) therapeutic compositions may be inactivated before producing an effect, i.e. such as proteolytic degradation of the peptide or protein; (2) the therapeutic composition may not reach the target area, i.e. the peptide or protein may not be able to cross the mucosa or may be adsorbed or processed by fluids, cells and tissues where the peptide or protein has no effect, (3) other functional properties, known or unknown, may make the therapeutic composition unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment (See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. App. & Inter. 1992)).

The relative skill of those in the art:

The relative skill of those in the art is high; however with respect to the *a priori* knowledge as to predicting the effect which HGF's physiological mechanism (neovascularization inhibiting hyperpermeability) may have upon complex neurological behavioral disorders/disease states (learning, memory, dementia) *and* in all mammals (without limitation to the health status of the mammal) is beyond the purview of the skilled artisan.

The amount of direction or guidance presented and the presence or absence of working examples:

The specification has provided examples of treating a mammal, male Wistar rats, having a microsphere embolism (ME)-induced cerebrovascular accidents or ischemia, the treatment comprising injecting a solution of HGF into the right cerebral ventricle, resulting in (a) inhibition of the magnitude of loss of memory/learning and (b) inhibition of adventitious hyperpermeability of FITC-albumin from the vascular milieu; however, the specification does not provide a sufficient number of working examples to be representative of inhibition of all vascular hyperpermeable events or all neurological syndromes/diseases/functions and in all instances.

Furthermore, the evaluation model of a (Morris) maze escape test requires sensory (visual/occipital), cognitive (memory), and ambulatory (motor) skills in the evaluation. Thus seeing, remembering, and maneuvering the maze are simultaneously tested. As evidenced by WATERMAZE ("Morris Watermaze" retrieved from <http://www.watermaze.org> (accessed 12/20/2007.), teaches that albino rats have impaired vision and underperform in the watermaze test versus hooded rats (see page 2, "The Rodents", ¶2). Whereas the induced embolism (occlusion of the right external carotid and right pterygopalatine artery) is not identified as discriminatory or isolated to memory- versus motor-/occipital-neural cells.

In view of the above, there is insufficient guidance as to how the range of claimed cognitive skill sets (memory, learning, dementia) may be identified in an evaluation which also requires physical skills and which may benefit from sensory skills, especially when the subjects are physically, potentially visually, and cognition-impaired subjects (i.e. the rat model exemplified is indicative of memory, learning, visual, or coordination impairment *or* a combination thereof but does not provide a method of identifying and contrasting any isolated impairment and uses a physical skill component in the test).

The quantity of experimentation necessary:

Considering the state of the art and the high unpredictability and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to make and use the invention commensurate in scope with the claims.

It is the Examiner's position that one skilled in the art could not practice the invention commensurate in the scope of the claims without undue experimentation. It is also noted, considering the *a priori* unpredictability in the art with regard to correlating the behavioral symptoms with the physiological mechanism of HGF, that treatment to improve dementia and memory and learning functions are not enabled in the manner instantly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 18, and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by AKIMOTO (**AI**: PTO-1449 4/13/2006) *or* MORISHITA (**AF**: PTO-1449 4/13/2006) or NAKAMURA (**AA**:PTO-1449 4/13/2006: US 6.699,837).

The general teachings of the claims are above.

AKIMOTO anticipates the claims by teaching administering HGF to a mammal (mouse). Although Akimoto is directed to the intended use of memory improvement, to the extent that the same organism (mammal) and the same active agent (HGF) requiring the same method step of administering are instantly claimed and also taught by Akimoto, following the same active method step would thus intrinsically produce the same results of (cerebro)vascular inhibitions and functional improvement.

MORISHITA anticipates the claims by teaching administering HGF (HGF *per se* and the HGF-encoding gene/liposome combination)(English Abstract).

Please note, while discovery of the biological mechanism behind the administration of a known bioactive compound is clearly publishable in a peer-review journal, the criteria for patenting claims are distinct from publication criteria. For example, if the active step of the method is the same and the subject is the same (e.g. treating a mammal with HGF), then the claimed method can be anticipated or made obvious by the prior art, even if the prior art does not recognize or appreciate this mechanism as long as the compound and/or dose administered, mode of administration, subject, etc. are the same as in the method disclosed in the prior art.

If this were not so, one patent might issue with a one step claim of administering the a compound to a subject in order to empirically treat a specific disease which is result of a contemporaneously unknown, disordered mechanism or pathway; and, then upon later discovery of the mechanism of the disorder, additional patents could issue with one-step claims directed to the administration of the same compound to the same subject in order to modulate the

specifically disordered mechanism or pathway. This would lead to multiple patents with essentially the same invention being patented, merely being couched in different words.

NAKAMURA (**AA:** WO/95/07709 A1) anticipates the claims by teaching the method of administering HGF and the intended uses of treating dementia and cerebral stroke/infarction (e.g. as shown in the English equivalent (**BA**: US 6,699,837) page 15, ¶ 1; claims 5,7,8,10, 12, and 13). To the extent Nakamura may be silent with respect to all of the possible effects of the administration of HGF, since the properties of HGF are intrinsic to the compound, administration of the compound to a subject would be expected to have an intrinsic effect/response in similar method conditions (e.g. "treating a mammal with HGF", (**BA**: US 6,699,837) page 15, ¶ 1; claims 5,7,8,10, 12, and 13).

Please note, as discussed above, while discovery of the biological mechanism behind the administration of a known bioactive compound is clearly publishable in a peer-review journal, the criteria for patenting claims are distinct from publication criteria. For example, if the active step of the method is the same and the subject is the same, then the claimed method can be anticipated or made obvious by the prior art, even if the prior art does not recognize or appreciate this mechanism as long as the compound and/or dose administered, mode of administration, subject, etc. are the same as in the method disclosed in the prior art.

If this were not so, one patent might issue with a one step claim of administering the a compound to a subject in order to empirically treat a specific disease which is result of a contemporaneously unknown, disordered mechanism or pathway; and, then upon later discovery of the mechanism of the disorder, additional patents could issue with one-step claims directed to the administration of the same compound to the same subject in order to modulate the

specifically disordered mechanism or pathway. This would lead to multiple patents with essentially the same invention being patented, merely being couched in different words.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17, 18, and 25-27 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5, 7, 8, 10, 12, and 13 of U.S. Patent No. 6,699,837 (**BA**: PTO-1449 4/13/206). Although the conflicting claims are not identical in reciting the intended use/effect of the method, the claims are not patentably distinct from each other because both claims require the same active step using (administering), the same compound (HGF), and are claimed/disclosed to treat the same conditions/populations (e.g. dementia, cerebral stoke/infarcts). Although the instant claims are drawn to *potentially* new or previously unrecited effects of the known HGF compound, since the compound used is inseparable from its properties and since the method of treating (administering HGF) for

treatment of cerebrovascular/ dementia conditions above is known in the issued '837 patent and prior art, absent evidence to the contrary, it would be *prima facie* obvious that practicing the treatment method of the patented '837 method would have expectedly and intrinsically functioned in the manner(s) of the instantly claimed/disclosed method.

The examiner has identified in the above rejection, copending Application(s) and/or issued U.S. Patent(s) which were copending at the time of the instant Application. which may be rejected under the Double Patenting criteria above; however, because of Applicant's prolific Patent and Application portfolio, Applicant's cooperation to identify all relevant presently copending Applications and Patents which were copending at the time of the instant Application, *and to include said relevant Applications and Patents on any terminal disclaimer filed.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aaron J. Kosar whose telephone number is (571) 270-3054. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday,EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Aaron Kosar
Examiner, Art Unit 1651

SANDRA E. SAUCIER
PRIMARY EXAMINER